.TENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
|---|---|---|
| SCB/51639001 | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/GB 99/ 04380 | 22/12/1999 | 23/12/1998 |
| Applicant | | |
| JANSSEN PHARMACEUTICA N.V. et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

# INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/GB 99/04380

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | SCHUETZ E G ET AL: "Modulators and substrates of P-glycoprotein and cytochrome P4503A coordinately up-regulate these proteins in human colon carcinoma cells." MOLECULAR PHARMACOLOGY, (1996 FEB) 49 (2) 311-8. , XP000906895 the whole document<br>---<br>-/-- | 1-4, 7-10, 17-28, 32-37 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 4 May 2000 | 19/05/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Molina Galan, E |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | DATABASE MEDLINE 'Online!<br>US NATIONAL LIBRARY OF MEDICINE (NLM),<br>BETHESDA, MD, US<br>YOKOI T ET AL: "Genetic polymorphism of drug metabolizing enzymes: new mutations in CYP2D6 and CYP2A6 genes in Japanese."<br>retrieved from STN<br>Database accession no. 1998428039<br>XP002136986<br>abstract<br>& NIPPON YAKURIGAKU ZASSHI. FOLIA PHARMACOLOGICA JAPONICA, (1998 JUL) 112 (1) 5-14. REF: 45 , | 1-4,<br>7-10,<br>25-28,<br>32-37 |
| X | JOUNAIDI, YOUSSEF ET AL: "Sequence of the 5'-flanking region of CYP3A5: comparative analysis with CYP3A4 and CYP3A7"<br>BIOCHEM. BIOPHYS. RES. COMMUN. (1994), 205(3), 1741-7 , XP002136985<br>cited in the application<br>the whole document | 17-24 |
| A | EP 0 463 395 A (HOFFMANN LA ROCHE)<br>2 January 1992 (1992-01-02) | |
| A | WO 95 30772 A (KAMATAKI TETSUYA ;OTSUKA PHARMA CO LTD (JP))<br>16 November 1995 (1995-11-16) | |
| A | YOKOI T ET AL: "Genetic polymorphism of drug metabolizing enzymes: new mutations in CYP2D6 and CYP2A6 genes in Japanese."<br>PHARMACEUTICAL RESEARCH, (1998 APR) 15 (4) 517-24. REF: 63 , XP000906892 | |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/04380

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0463395 A | 02-01-1992 | AU 645091 B | 06-01-1994 |
| | | CA 2045012 A | 23-12-1991 |
| | | JP 5211895 A | 24-08-1993 |
| | | NZ 238610 A | 25-11-1993 |
| | | US 5648482 A | 15-07-1997 |
| | | US 5844108 A | 01-12-1998 |
| | | DE 69126064 D | 19-06-1997 |
| | | DE 69126064 T | 28-08-1997 |
| | | ES 2103756 T | 01-10-1997 |
| WO 9530772 A | 16-11-1995 | JP 7298900 A | 14-11-1995 |
| | | CA 2189638 A | 16-11-1995 |
| | | CN 1151763 A | 11-06-1997 |
| | | EP 0759476 A | 26-02-1997 |

European Patent Office

# EUROPEAN SEARCH REPORT

Application Number

EP 91 10 8867

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
|---|---|---|---|
| P,X | THE LANCET, vol. 336, 1st September 1990, pages 529-532, London, GB; M. HEIM et al.: "Genotyping of poor metabolisers of debrisoquine by allele-specific PCR amplification" * Whole article * | 1-5,9-11, 14-16, 19-24 | C 12 Q 1/68<br>C 07 H 21/04<br>C 12 N 15/10 |
| A | CHEMICAL ABSTRACTS, vol. 112, 1990, page 266, abstract no. 71647h, Columbus, Ohio, US; & US-A-292 815 (UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES) 15-07-1989 * Abstract * | 1,3,14,16, 21 | |
| A | NUCLEIC ACIDS RESEARCH, vol. 17, no. 7, 11th April 1989, pages 2503-2516, Eynsham, Oxford, GB; C.R. NEWTON et al.: "Analysis of any point mutation in DNA. The amplification refractory mutation system (ARMS)" * Abstract * | 1 | |
| D,A | THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 8, 15th March 1990, pages 4630-4634, American Society for Biochemistry and Molecular Biology, Inc., Baltimore, US; S. OHSAKO et al.: "Cloning and expression of cDNAs for polymorphic and monomorphic arylamine N-acetyltransferases from human liver" * Figure 1 * | 8,13 | TECHNICAL FIELDS SEARCHED (Int. Cl.5)<br>C 12 Q |
| D,A | NUCLEIC ACIDS RESEARCH, vol. 17, no. 9, 1989, page 3589; M. BLUM et al.: "Nucleotide sequence of a full-length cDNA for arylamine N-acetyltransferase from rabbit liver" * Page 3589 * | 8,13 | |
| D,A | AM. J. HUM. GEN., vol. 45, 1989, pages 889-904, Chicago, US; S. KIMURA et al.: "The human debrisoquine 4-hydroxylase (CYP2D) locus: sequence and identification of the polymorphic CYP2D6 gene, a related gene, and a pseudogene" | | |

The present search report has been drawn up for all claims

| Place of search | Date of completion of search | Examiner |
|---|---|---|
| The Hague | 09 August 91 | MOLINA GALAN E. |

CATEGORY OF CITED DOCUMENTS

- X: particularly relevant if taken alone
- Y: particularly relevant if combined with another document of the same catagory
- A: technological background
- O: non-written disclosure
- P: intermediate document
- T: theory or principle underlying the invention
- E: earlier patent document, but published on, or after the filing date
- D: document cited in the application
- L: document cited for other reasons
- &: member of the same patent family, corresponding document

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/04380

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | SCHUETZ E G ET AL: "Modulators and substrates of P-glycoprotein and cytochrome P4503A coordinately up-regulate these proteins in human colon carcinoma cells." MOLECULAR PHARMACOLOGY, (1996 FEB) 49 (2) 311-8. , XP000906895 the whole document<br>---<br>-/-- | 1-4, 7-10, 17-28, 32-37 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 4 May 2000 | 19/05/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Molina Galan, E |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/GB 99/04380

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0463395 A | 02-01-1992 | AU 645091 B | 06-01-1994 |
| | | CA 2045012 A | 23-12-1991 |
| | | JP 5211895 A | 24-08-1993 |
| | | NZ 238610 A | 25-11-1993 |
| | | US 5648482 A | 15-07-1997 |
| | | US 5844108 A | 01-12-1998 |
| | | DE 69126064 D | 19-06-1997 |
| | | DE 69126064 T | 28-08-1997 |
| | | ES 2103756 T | 01-10-1997 |
| WO 9530772 A | 16-11-1995 | JP 7298900 A | 14-11-1995 |
| | | CA 2189638 A | 16-11-1995 |
| | | CN 1151763 A | 11-06-1997 |
| | | EP 0759476 A | 26-02-1997 |

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| SCB/51639001 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/GB99/04380 | 22/12/1999 | 23/12/1998 |
| International Patent Classification (IPC) or national classification and IPC<br>C12Q1/68 | | |
| Applicant<br>JANSSEN PHARMACEUTICA N.V. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 29/05/2000 | 30.03.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Knudsen, H<br>Telephone No. +49 89 2399 8696 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/04380

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-40 as originally filed

**Claims, No.:**

1-39 as originally filed

**Drawings, sheets:**

1/15-15/15 as originally filed

**Sequence listing part of the description, pages:**

1-4, filed with the letter of 06.03.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:
   **see separate sheet**

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   **see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Yes: | Claims 1-39 |
| | No: | Claims |

| | | | |
|---|---|---|---|
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-39 |
| Industrial applicability (IA) | Yes: | Claims | 1-39 |
| | No: | Claims | |

2. Citations and explanations
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
**see separate sheet**

## ITEM I:

It is not possible for the International Examining Authority to determine whether the pages of the sequence listing filed together with letter of 06 March 2000 meet the requirements of Article 34(2)(b) PCT and the examination is therefore carried out on the basis of the sequences contained in the originally filed description.

## ITEM IV:

The claims can be divided into the following three groups of claims:

I: Claims 1-24 and 26-31 concern the determination of the metabolism phenotype of subjects by screening for polymorphisms.

II: Claim 25 concern the identification of toxic effects of a test compound by contacting the test compound with low and high metabolising cells.

III: Claims 32-39 concern methods for identifying polymorphisms with influence on the activity of the CYP3A5 gene.

The only common feature of the said groups of claims is the polymorphism which influence the metabolic activity of CYP3A5. However, this concept is known from D2 (see Item V) and therefore cannot constitute a single common inventive concept. Thus, the present claims lack unity-of-invention.

## ITEM V:

The cited prior art documents are

**D1: Molecular Pharmacology, vol.49(2), p.311-318, (1996)**

**D2: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US retrieved from STN Database accession no. 1998428039 & Nippon Yakurigaku Zasshi. Folia Pharmacologica Japonica, vol.112(1), p.5-14, (July 1998)**

**D3: Biochem. Biophys. Res. Commun., vol.205(3), p.1741-1747, (1994)**

NOVELTY & INVENTIVE STEP:

5.1 The closest prior art is described in D2 which reports that a genetic polymorphism in CYP3A5 causes a poor metabolising phenotype. The subject-matter of claims 1 and 2 differs from D2 only in that the polymorphism is positioned in the transcription regulatory region. However, D1 (p.316, right col., lines 4-6) discloses that CYP3A5 is expressed in only 25-30 % of the population and D3 (p.1741, penultimate line) continues that CYP3A5 mRNA and protein is found in only 10-30% of Caucasian adults. To the skilled person it would therefore be obvious that a polymorphism in the CYP3A5 gene, which influences the drug metabolism, may be situated in the regulatory region and not in the expressed protein.

The applicant argues that a polymorphism which cause a difference in gene expression need not be present in the transcription regulatory region, but may influence expression by causing an unstable RNA or defects in the protein itself.

The IPEA is however of the opinion that a single nucleotide polymorphism (SNP) in the region coding for the expressed protein will generally cause a similar protein with reduced activity to be produced whereas a SNP in a transcription regulatory region such as the promoter often cause complete loss or very much reduced transcription of the adjacent genes, due to the high specificity of the RNA polymerase - promoter interaction (see eg the founding textbook "Genes, Ed. B.Lewin, John Wiley & Sons, (1983), p.181"). The IPEA therefore does not argue that it is immediately apparent to the skilled person from D1 that a mutation is found in the transcription regulatory region, but maintains its views that D1 and D2 in combination leads the skilled person, who wishes to find the polymorphism influencing the differentiated expression of CYP3A5, to study the transcription regulatory region of CYP3A5.

For the skilled person, who wishes to solve the problem of identifying the drug metabolising activity of subjects, it would therefore be obvious to identify subjects having a high or low drug metabolising phenotype by the method mentioned in claims 1 and 2. Thus, claims 1 and 2 do not involve an inventive step.

5.2 Recognition sites for transcription factors, the activator protein-3 motif and the basic transcription element are well-known regions of the regulatory region of the CYP3A5 gene (see D3, page 1746, 2nd paragraph) and it would therefore be obvious for the skilled person to look for the polymorphism in these regions, especially as D3 shows that the two clones used therein have different sequences in these regions. Claims 3-4 therefore do not appear to be inventive.

5.3 The clones studied in D3 have different sequences at the positions -475 and -147 and D3 therefore indicates the presence of SNPs at these positions. Though D3 also indicates other SNPs in the 5'-flanking region of CYP3A5, the SNPs suggested at positions -475 and -147 are the only polymorphisms in regions known to play a role in transcription regulation (see positions -44 and -358 in Figure 2). The IPEA therefore considers that D3 in combination with D2 would lead the skilled person to study whether the mutations at -475 and -147 play a role in the differences for the drug metabolic activity of the CYP3A5 gene. Claims 5 and 6 therefore are not considered inventive.

5.4 The feature of claim 7 is commonly used in the art and therefore does not add anything inventive to the method of claim 1.

5.5 Also the steps of the method of claim 8 is common in the art, its use in the identification of polymorphic variants in a transcription regulatory region therefore does not involve anything inventive for the reasons given for claims 1-6. Thus, claims 8-16 are not considered inventive.

5.6 The design of a primer which binds to a polymorphic variant or wild type nucleotide in a specific region with known sequence is routinely carried out by the skilled person and claims 17-24 therefore lack an inventive step for the same reasons as claims 1-6.

5.7 D2 describe the treatment of CYP2A6 (another cytochrome gene) containing cells with a drug and the identification of poorly metabolising cells on the basis of the effects of the drug on the cell. The method of claim 25 differs from D2 in that it concerns drugs metabolised by CYP3A5 and in that the method is used to identify the toxic effects of the test compound. In the light of D2, it appears to be obvious

that a drug metabolizing assay for CYP3A5 can be designed analogously to the assay for CYP2A6 and that the effects of the drug on a cell in which CYP3A5 does not metabolise the drug can be studied. The applicant argues that CYP3A5 and CYP2A6 do not metabolize the same drugs and are therefore not equivalents. The IPEA is, however, of the opinion that the drug-specificity of CYP3A5 is known to the skilled person (see abstract of reference 36 in D1, "Mol. Pharmacol., vol.38(2), p.207- 213, (1990)") and it would therefore not require an inventive skill to design an assay in which the drug-metabolizing effect of CYP3A5 in cells was tested.

5.8 The method of claim 26 differs from D2 in that it is used to diagnose the susceptibility of an individual to a disease associated with environmental toxins or procarcinogens. However, it is well-known to the skilled person that many toxins and procarcinogens are oxidised by the cytochrome system the same way as drugs. It would therefore be obvious to the skilled person that the test system described in D2 for CYP2A6 can be applied analogously for CYP3A5 for diagnosing susceptibility to diseases associated with toxins or procarcinogens. Claims 26-31 therefore do not appear to be inventive.

5.9 The methods of claims 32-35 do not go beyond what is routinely carried out in the investigation of regulatory regions for genes and therefore lack an inventive step for the same reasons as claims 1-2. Claims 36-39 do not add anything inventive to these claims for the reasons outlined for claims 3-6.

INDUSTRIAL APPLICABILITY:

5.10 The subject-matter of claims 1-39 is considered industrially applicable.

## ITEM VII:

7.1 Contrary to the requirements of Rule 5(a)(ii) PCT, the closest prior art documents D1 and D2 are not identified in the description and the relevant background art disclosed therein is not briefly discussed.

7.2 Contrary to the PCT Guidelines C-II 4.16-4.17, terms, eg "BigDye", used in the description have not been identified as registered trade marks.

# ITEM VIII:

8.1 The present application's description contains data only for the -147 and -475 polymorphisms which are shown to be linked. There is no evidence that any polymorphism which is not linked with the above have any influence on the drug metabolic behaviour of the subject.

8.2 It is not clear how oligonucleotides with a certain binding specificity can be selected for unknown polymorphisms, present claim 8 therefore appears to be directed to the identification of known polymorphic variants in a subject. Thus, claim 8 contains all features of claim 7 and is, in fact, dependent thereon.

8.3 The oligonucleotide of claim 17 is defined as being capable of hybridising specifically to wild-type or polymorphic variant of a transcription regulatory region of the sequence encoding CYP3A5. For the unknown polymorphisms this leads to an undefined scope of the claim. Claims 17-19 and 22-24 are therefore unacceptable due to lack of clarity.

8.4 The claims should only exceptionally refer to the description or drawings (Rule 6.2 PCT). Claim 21 contravenes this rule.

8.5 The description does not appear to mention the effects of a test compound on cells which can be measured according to claim 25. Claim 25 therefore appears to lack support in the description.

8.6 The application does not appear to mention specifically environmental toxins or procarcinogens which are metabolised by CYP3A5 and claim 26 therefore is not sufficiently supported by the description.

8.7 The number of independent claims is too high, this causes a lack of clarity for the set of claims as a whole.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

# PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>09 August 2000 (09.08.00) | |
| **International application No.**<br>PCT/GB99/04380 | **Applicant's or agent's file reference**<br>SCB/51639001 |
| **International filing date** (day/month/year)<br>22 December 1999 (22.12.99) | **Priority date** (day/month/year)<br>23 December 1998 (23.12.98) |
| **Applicant**<br>PAULUSSEN, Aimee, Dymphne, Catherine et al | |

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

29 May 2000 (29.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|---|
| **The International Bureau of WIPO**<br>**34, chemin des Colombettes**<br>**1211 Geneva 20, Switzerland** | Authorized officer<br>S. Mafla |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

# PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| SCB/51639001 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/GB99/04380 | 22/12/1999 | 23/12/1998 |
| International Patent Classification (IPC) or national classification and IPC<br>C12Q1/68 | | |
| Applicant<br>JANSSEN PHARMACEUTICA N.V. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

| | | |
|---|---|---|
| I | ☒ | Basis of the report |
| II | ☐ | Priority |
| III | ☐ | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| IV | ☒ | Lack of unity of invention |
| V | ☒ | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement |
| VI | ☐ | Certain documents cited |
| VII | ☒ | Certain defects in the international application |
| VIII | ☒ | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 29/05/2000 | 30.03.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Knudsen, H<br>Telephone No. +49 89 2399 8696 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/04380

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-40 as originally filed

**Claims, No.:**

1-39 as originally filed

**Drawings, sheets:**

1/15-15/15 as originally filed

**Sequence listing part of the description, pages:**

1-4, filed with the letter of 06.03.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:
   **see separate sheet**

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   **see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Yes: | Claims 1-39 |
| | No: | Claims |

| | | | |
|---|---|---|---|
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-39 |
| Industrial applicability (IA) | Yes: | Claims | 1-39 |
| | No: | Claims | |

2. Citations and explanations
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
**see separate sheet**

## ITEM I:

It is not possible for the International Examining Authority to determine whether the pages of the sequence listing filed together with letter of 06 March 2000 meet the requirements of Article 34(2)(b) PCT and the examination is therefore carried out on the basis of the sequences contained in the originally filed description.

## ITEM IV:

The claims can be divided into the following three groups of claims:

I: Claims 1-24 and 26-31 concern the determination of the metabolism phenotype of subjects by screening for polymorphisms.

II: Claim 25 concern the identification of toxic effects of a test compound by contacting the test compound with low and high metabolising cells.

III: Claims 32-39 concern methods for identifying polymorphisms with influence on the activity of the CYP3A5 gene.

The only common feature of the said groups of claims is the polymorphism which influence the metabolic activity of CYP3A5. However, this concept is known from D2 (see Item V) and therefore cannot constitute a single common inventive concept. Thus, the present claims lack unity-of-invention.

## ITEM V:

The cited prior art documents are

**D1: Molecular Pharmacology, vol.49(2), p.311-318, (1996)**

**D2: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US retrieved from STN Database accession no. 1998428039 & Nippon Yakurigaku Zasshi. Folia Pharmacologica Japonica, vol.112(1), p.5-14, (July 1998)**

**D3: Biochem. Biophys. Res. Commun., vol.205(3), p.1741-1747, (1994)**

NOVELTY & INVENTIVE STEP:

5.1 The closest prior art is described in D2 which reports that a genetic polymorphism in CYP3A5 causes a poor metabolising phenotype. The subject-matter of claims 1 and 2 differs from D2 only in that the polymorphism is positioned in the transcription regulatory region. However, D1 (p.316, right col., lines 4-6) discloses that CYP3A5 is expressed in only 25-30 % of the population and D3 (p.1741, penultimate line) continues that CYP3A5 mRNA and protein is found in only 10-30% of Caucasian adults. To the skilled person it would therefore be obvious that a polymorphism in the CYP3A5 gene, which influences the drug metabolism, may be situated in the regulatory region and not in the expressed protein.

The applicant argues that a polymorphism which cause a difference in gene expression need not be present in the transcription regulatory region, but may influence expression by causing an unstable RNA or defects in the protein itself.

The IPEA is however of the opinion that a single nucleotide polymorphism (SNP) in the region coding for the expressed protein will generally cause a similar protein with reduced activity to be produced whereas a SNP in a transcription regulatory region such as the promoter often cause complete loss or very much reduced transcription of the adjacent genes, due to the high specificity of the RNA polymerase - promoter interaction (see eg the founding textbook "Genes, Ed. B.Lewin, John Wiley & Sons, (1983), p.181"). The IPEA therefore does not argue that it is immediately apparent to the skilled person from D1 that a mutation is found in the transcription regulatory region, but maintains its views that D1 and D2 in combination leads the skilled person, who wishes to find the polymorphism influencing the differentiated expression of CYP3A5, to study the transcription regulatory region of CYP3A5.

For the skilled person, who wishes to solve the problem of identifying the drug metabolising activity of subjects, it would therefore be obvious to identify subjects having a high or low drug metabolising phenotype by the method mentioned in claims 1 and 2. Thus, claims 1 and 2 do not involve an inventive step.

5.2 Recognition sites for transcription factors, the activator protein-3 motif and the basic transcription element are well-known regions of the regulatory region of the CYP3A5 gene (see D3, page 1746, 2nd paragraph) and it would therefore be obvious for the skilled person to look for the polymorphism in these regions, especially as D3 shows that the two clones used therein have different sequences in these regions. Claims 3-4 therefore do not appear to be inventive.

5.3 The clones studied in D3 have different sequences at the positions -475 and -147 and D3 therefore indicates the presence of SNPs at these positions. Though D3 also indicates other SNPs in the 5'-flanking region of CYP3A5, the SNPs suggested at positions -475 and -147 are the only polymorphisms in regions known to play a role in transcription regulation (see positions -44 and -358 in Figure 2). The IPEA therefore considers that D3 in combination with D2 would lead the skilled person to study whether the mutations at -475 and -147 play a role in the differences for the drug metabolic activity of the CYP3A5 gene. Claims 5 and 6 therefore are not considered inventive.

5.4 The feature of claim 7 is commonly used in the art and therefore does not add anything inventive to the method of claim 1.

5.5 Also the steps of the method of claim 8 is common in the art, its use in the identification of polymorphic variants in a transcription regulatory region therefore does not involve anything inventive for the reasons given for claims 1-6. Thus, claims 8-16 are not considered inventive.

5.6 The design of a primer which binds to a polymorphic variant or wild type nucleotide in a specific region with known sequence is routinely carried out by the skilled person and claims 17-24 therefore lack an inventive step for the same reasons as claims 1-6.

5.7 D2 describe the treatment of CYP2A6 (another cytochrome gene) containing cells with a drug and the identification of poorly metabolising cells on the basis of the effects of the drug on the cell. The method of claim 25 differs from D2 in that it concerns drugs metabolised by CYP3A5 and in that the method is used to identify the toxic effects of the test compound. In the light of D2, it appears to be obvious

that a drug metabolizing assay for CYP3A5 can be designed analogously to the assay for CYP2A6 and that the effects of the drug on a cell in which CYP3A5 does not metabolise the drug can be studied. The applicant argues that CYP3A5 and CYP2A6 do not metabolize the same drugs and are therefore not equivalents. The IPEA is, however, of the opinion that the drug-specificity of CYP3A5 is known to the skilled person (see abstract of reference 36 in D1, "Mol. Pharmacol., vol.38(2), p.207- 213, (1990)") and it would therefore not require an inventive skill to design an assay in which the drug-metabolizing effect of CYP3A5 in cells was tested.

5.8 The method of claim 26 differs from D2 in that it is used to diagnose the susceptibility of an individual to a disease associated with environmental toxins or procarcinogens. However, it is well-known to the skilled person that many toxins and procarcinogens are oxidised by the cytochrome system the same way as drugs. It would therefore be obvious to the skilled person that the test system described in D2 for CYP2A6 can be applied analogously for CYP3A5 for diagnosing susceptibility to diseases associated with toxins or procarcinogens. Claims 26-31 therefore do not appear to be inventive.

5.9 The methods of claims 32-35 do not go beyond what is routinely carried out in the investigation of regulatory regions for genes and therefore lack an inventive step for the same reasons as claims 1-2. Claims 36-39 do not add anything inventive to these claims for the reasons outlined for claims 3-6.

INDUSTRIAL APPLICABILITY:

5.10 The subject-matter of claims 1-39 is considered industrially applicable.

## ITEM VII:

7.1 Contrary to the requirements of Rule 5(a)(ii) PCT, the closest prior art documents D1 and D2 are not identified in the description and the relevant background art disclosed therein is not briefly discussed.

7.2 Contrary to the PCT Guidelines C-II 4.16-4.17, terms, eg "BigDye", used in the description have not been identified as registered trade marks.

## ITEM VIII:

8.1 The present application's description contains data only for the -147 and -475 polymorphisms which are shown to be linked. There is no evidence that any polymorphism which is not linked with the above have any influence on the drug metabolic behaviour of the subject.

8.2 It is not clear how oligonucleotides with a certain binding specificity can be selected for unknown polymorphisms, present claim 8 therefore appears to be directed to the identification of known polymorphic variants in a subject. Thus, claim 8 contains all features of claim 7 and is, in fact, dependent thereon.

8.3 The oligonucleotide of claim 17 is defined as being capable of hybridising specifically to wild-type or polymorphic variant of a transcription regulatory region of the sequence encoding CYP3A5. For the unknown polymorphisms this leads to an undefined scope of the claim. Claims 17-19 and 22-24 are therefore unacceptable due to lack of clarity.

8.4 The claims should only exceptionally refer to the description or drawings (Rule 6.2 PCT). Claim 21 contravenes this rule.

8.5 The description does not appear to mention the effects of a test compound on cells which can be measured according to claim 25. Claim 25 therefore appears to lack support in the description.

8.6 The application does not appear to mention specifically environmental toxins or procarcinogens which are metabolised by CYP3A5 and claim 26 therefore is not sufficiently supported by the description.

8.7 The number of independent claims is too high, this causes a lack of clarity for the set of claims as a whole.